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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 38/21, C07K 14/47, A61K 38/17 // (A61K 38/21, 38:17)

A2

(11) International Publication Number: WO 95/30435

(43) International Publication Date: 16 November 1995 (16.11.95)

(21) International Application Number: PCT/US95/05605

(22) International Filing Date: 4 May 1995 (04.05.95)

(30) Priority Data:

08/241,246	10 May 1994 (10.05.94)	US
08/328,224	25 October 1994 (25.10.94)	US

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
Without international search report and to be republished upon receipt of that report.

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(54) Title: COMPOSITIONS AND TREATMENT FOR MULTIPLE SCLEROSIS

(57) Abstract

The present invention provides compositions and methods for treating multiple sclerosis. Compositions of the invention comprise at least one peptide or modified peptide of myelin basic protein (MBP) which comprises at least one T cell epitope, and IFN-β in an appropriate pharmaceutically acceptable medium for either oral, subcutaneous or intravenous administration. Methods of the inven include treatment of individuals who either have MS or are suspected of being susceptible to MS by administering a therapeutically effective amount of a composition of the invention or by administering in a therapeutic regimen, a composition comprising at least one peptide or modified peptide of MBP which comprises at least one T cell epitope and further administering IFN-β.

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COMPOSITIONS AND TREATMENT FOR MULTIPLE SCLEROSIS

Background of the Invention

Autoimmune diseases are a significant human health problem and are relatively poorly understood. As there is no microbial or viral culprit apparently directly responsible, prevention, treatment and diagnosis of such diseases must be based on the etiology of the disease. This invariably involves a complex series of reactions of endogenous metabolic intermediates, structural components, cells and so forth. Implicit however in the nature of an autoimmune condition is the notion that at least one autoantigen must be involved in creating the sequence of events that results in the symptoms. Autoimmune demyelinating diseases such as multiple sclerosis are no exception.

A commonly used animal model for human multiple sclerosis is experimental allergic encephalomyelitis (EAE), a demyelinating disease of the central nervous system which can be induced in susceptible strains of mice by immunization with myelin basic protein (MBP) or its immunodominant T cell determinants (i.e. T cell epitopes). MBP is one of the presumed autoantigens in multiple sclerosis (MS) and has been epitope-mapped in both human (Ota et al., *Nature*, **346**:183-187 (1990)) and rodent (Zamvil et al., *Nature*, **324**:258-260 (1986)) systems. Ota et al., *supra* have identified a major T cell epitope recognized by MS patients, MBP amino acid residues 84-102. Minor epitopes (MBP amino acid residues 143-168, 61-82, 124-142 and 31-50 recognized by T cells from MS patients were also described. Zamvil et al., *supra* have shown that MBP amino acid residues 1-11 contain the major T cell epitope(s) causing EAE, in susceptible rodent strains.

Over the past decade, it has become apparent that peptides corresponding to the major T cell epitopes of native protein antigens can be used to induce T cell non responsiveness to themselves or to the native protein antigen. Studies by Gaur et al., *Science*, **258**:1491-1494 have shown that T cell epitopes of MBP induce reduced T cell responsiveness to MBP in adult mice. In these studies, tolerance to synthetic peptides corresponding to the major immunodominant determinants of MBP (Ac 1-11 and 35-47) or the entire MBP by using an emulsion of the peptide or protein in non-immunogenic form (incomplete Freund's adjuvant) as described previously for tolerance induction to other proteins or peptides (F. Ria et al., *Nature*, **343**:381 (1990)). This reduced T cell responsiveness which was induced by the administration

of MBP T cell epitopes was able to prevent MBP-induced EAE. However, these studies showed that Ac 1-11, the more dominant of the two epitopes, induced only approximately a 50% decrease in subsequent T cell response to MBP, and the less immunogenic peptide aa 35-47 induced only approximately a 20% decrease in subsequent response to MBP. The mixture of the two peptides together provided a higher decrease in subsequent T cell response to MBP.

In a completely different approach to the treatment of MS, clinical studies have shown that interferons (IFNs) have shown some promise for treating MS. It has been shown that administration of IFN-γ promotes exacerbation of MS, whereas recombinant IFN-β has been shown in controlled clinical trials to suppress them (Hillel and Bever, *J. Neuroimmunology*, **46**:155-164 (1993)). However, despite evidence that administration of IFN-β to patients afflicted with MS declines the frequency and severity of attacks of MS, IFN-β is not the long awaited cure for MS that the medical community had hoped for (Arnason, *Neurology*, **43**:641-643 (1993)). In the clinical study described by Arnason, almost all patients treated with IFN-β had attacks eventually, and one in four deteriorated.

Summary of the Invention:

The present invention provides compositions and methods for treating multiple sclerosis. Compositions of the invention comprise at least one peptide or modified peptide of myelin basic protein (MBP) which comprise at least one T cell epitope, and IFN-β in an appropriate pharmaceutically acceptable medium for either oral, subcutaneous or intravenous administration. Methods of the invention include treatment of individuals who either have MS or are suspected of being susceptible to MS by administering a therapeutically effective amount of a composition of the invention or by administering in a therapeutic regimen, a composition comprising at least one peptide or modified peptide of MBP which comprises at least one T cell epitope and further administering IFN-β.

Brief Description of the Drawings

Fig. 1a is a graphic depiction of an experiment showing the effects of IFN-β on EAE in two groups of 10 (SJL x TLP) F_1 adult female mice who were induced EAE with guinea pig MBP in complete adjuvant plus pertussis toxin on day 0 and were administered either incomplete Freund's Adjuvant only (control) or were treated with 2000 units of IFN-β interperitoneally (i.p.) on days 9, 12, 16, and 20 (indicated by arrows on the x axis), the Y axis represents the mean clinical score (MCS) for each

group, 0=no clinical signs of EAE, 1=limp, unresponsive tail, 2=partial hindlimb paralysis, 3=complete hindlimb paralysis, 4=partial to complete forelimb paralysis and 5=moribund.

Fig. 1b is a graphic depiction of an experiment showing the effects of MBP peptide Ac 1-11 in two groups of 10 (SJL x TLP) F_1 adult female mice who were induced EAE with guinea pig MBP in complete adjuvant plus pertussis toxin on day 0 and were administered either PBS (control) or were treated with 250 nmol Ac 1-11 intravenously on days 10, 13, 17, and 21 (indicated by arrows on the x axis), the Y axis represents the average mean clinical score for each group as described for Fig. 1a.

Fig. 1c is a graphic depiction of an experiment showing the effects of MBP peptide Ac 1-11 administered in combination with IFN-β on EAE in two groups of 10 (SJL x TLP) F_1 adult female mice who were induced EAE with guinea pig MBP in complete adjuvant plus pertussis toxin on day 0 and were administered either PBS (control) or were treated with 250 nmol Ac 1-11 intravenously on days 10, 13, 17, and 21 (indicated by open arrows on the x axis), and were treated with 2000 units of IFN-β interperitoneally (i.p.) on days 9, 12, 16, and 20 (indicated by closed arrows on the x axis), the Y-axis indicates the mean clinical score as discussed for Fig. 1a.

Fig. 2 is a graphic depiction of an experiment showing the effects of various doses of IFN-β (10,000 units and 2,000 units respectively) on induced EAE in two groups of 10 (SJL x TLP) F_1 adult female mice who were induced EAE with guinea pig MBP plus pertussis toxin on day 0 and were administered either PBS (control) or were treated with 10,000 units and 2000 units respectively of IFN-β interperitoneally (i.p.) on days 9, 13, 16, (indicated by closed arrows on the x axis), the Y-axis indicates the mean clinical score as discussed for Fig. 1a.

Fig. 3 shows the full length amino acid sequence of human MBP.

Fig. 4 shows the amino acids sequences for selected MBP peptides useful in the practice of the instant invention.

Detailed Description of the Invention:

The present invention provides methods for treating multiple sclerosis comprising administering a therapeutically effective amount of at least one antigenic peptide of MBP in a treatment regimen which includes a therapeutically effective amount of IFN-β. As used herein the term "peptide" refers to an amino acid sequence

having fewer amino acid residues than the entire amino acid sequence of the protein from which the peptide was derived. The term "antigenic peptide" as used herein refers to any peptide comprising at least one T cell epitope or any portion of such peptide comprising at least one T cell epitope.

In referring to an epitope, the epitope will be the basic element, or smallest unit of recognition by a receptor, particularly immunoglobulins, histocompatibility antigens and T cell receptors, where the epitope comprises amino acids of the native protein such as the autoantigen which are essential to receptor recognition. T cell epitopes are believed to be involved in initiation and perpetuation of the autoimmune response. These T cell epitopes are thought to trigger early events at the level of the T helper cell by being presented by an appropriate HLA molecule on the surface of an antigen presenting cell, thereby stimulating the T cell subpopulations with the relevant T cell receptor for the epitope. These events lead to T cell proliferation, lymphokine secretion, local inflammatory reaction, recruitment of additional immune cells to the site of antigen/T cell interaction and activation of the B cell cascade leading to the production of antibodies.

Exposure of a subject to a peptide or protein which comprises at least one T cell epitope of the autoantigen may modify T cell subpopulations such that they become unresponsive to the autoantigen and do not participate in stimulating an immune response. In addition, administration of a protein or peptide which comprises at least one T cell epitope may modify the lymphokine secretion profile as compared with exposure to the naturally occurring autoantigen (e.g. result in a decrease or IL-4 and/or increase in IL-2 causing a modification of TH1 and TH2 populations). Furthermore, exposure to such a peptide may influence T cell subpopulations which normally participate in the response to the autoantigen such that these T cells are drawn away from the sites of normal exposure to the autoantigen (e.g. tissues of the central nervous system (CNS)) to the sites of therapeutic administration of the peptide derived therefrom. This redistribution of T cell subpopulations may ameliorate or reduce the ability of the individual's immune system to stimulate the usual immune response at the site of normal exposure to the autoantigen resulting in diminution of symptoms.

Any peptides derived from MBP which moderate response of a subject to MBP autoantigen may be included in the methods and compositions of the invention. Such peptides may be identified, for example, by examining the structure and selecting appropriate regions to be produced as peptides (via recombinant expression systems, synthetically or otherwise) to be examined for ability to influence T cell

responses to MBP, and selecting peptides containing epitopes recognized by these cells. Many human MBP peptides comprising T cell epitopes are described in the art.

Modified antigenic peptides are useful within the scope of the invention. For example, a peptide can be modified so that it maintains the ability to induce T cell anergy and bind MHC protein without the ability to induce a strong proliferative response or possibly, any proliferative response when administered in immunogenic form. In this instance, critical binding residues for the T cell receptor can be determined using known techniques (e.g. substitution of each residue and determination of the presence or absence of T cell reactivity). Those residues shown to be essential to interact with the T cell receptor can be modified by replacing the essential amino acid with another, preferably similar amino acid residue (a conservative substitution) whose presence is shown to enhance, diminish but not eliminate or not effect T cell reactivity. In addition, those amino acid residues which are not essential for T cell receptor interaction can be modified by being replaced by another amino acid whose incorporation may enhance, diminish but not eliminate, or not effect T cell reactivity. In addition, those amino acid residues which are not essential for T cell receptor interaction can be modified by being replaced by another amino acid whose incorporation may enhance diminish or not effect T cell reactivity but does not eliminate binding to relevant MHC.

Additionally, peptides of the invention can be modified by replacing an amino acid shown to be essential to interact with MHC protein complex with another preferably similar amino acid residue (conservative substitution) whose presence is shown to enhance, diminish but not eliminate or not effect T cell activity. In addition, amino acid residues which are not essential for interaction with the MHC protein complex can be modified by being replaced by another amino acid whose incorporation may enhance, not effect, or diminish but not eliminate T cell reactivity. Preferred amino acid substitutions for non-essential amino acids include but are not limited to substitutions with alanine, glutamic acid, or a methyl amino acid.

Another example of a modification of peptides is substitution of cysteine residues preferably with serine, threonine, leucine or glutamic acid to minimize dimerization via disulfide linkages. In addition peptides may be modified to increase the solubility of a peptide for use in buffered aqueous solutions such as pharmaceutically acceptable carriers or diluents by adding functional groups to the peptide, terminal portions of the peptide, or by not including hydrophobic T cell epitopes or regions containing hydrophobic epitopes in the peptides or hydrophobic regions of the protein or peptide. For example, to increase solubility, charged amino acids or charged amino acid pairs or triplets may be added to the carboxy or amino

terminus of the peptide. Examples of charged amino acids include arginine (R), lysine (K), histidine (H), glutamic acid (E), and aspartic acid (D).

Additionally peptides comprising "cryptic epitopes" may be determined and are also useful in the methods and compositions of the invention. Cryptic epitopes are those determinants in a protein antigen which, due to processing and presentation of the native protein antigen to the appropriate MHC molecule, are not normally revealed to the immune system. However, a peptide comprising a cryptic epitope is capable of causing T cells to become non-responsive, and when a subject is primed with the peptide, T cells obtained from the subject will proliferate *in vitro* in response to the peptide or the protein antigen from which the peptide is derived. Peptides which comprise at least one cryptic epitope derived from a protein antigen are referred to herein as "cryptic peptides". To confirm the presence of cryptic epitopes a T cell proliferation assay may be used as is known in the art in which antigen primed T cells are cultured *in vitro* in the presence of each peptide separately to establish peptide-reactive T cell lines. A peptide is considered to comprise at least one cryptic epitope if a T cell line can be established with a given peptide and T cells are capable of proliferation upon challenge with the peptide and the protein antigen from which the peptide is derived.

Antigenic peptides useful within in the compositions and methods of the present invention include the following peptides or portions thereof having residue numbers which correspond the amino acid residues of the human MBP protein shown in Fig. 3: a peptide comprising all or a portion of amino acid residues 84-106 of human MBP, a peptide comprising all or a portion of amino acid residues 84-102 of human MBP, a peptide comprising all or a portion of amino acid residues 89-101 of human MBP, a peptide comprising all or a portion of amino acid residues 140-172 of human MBP, a peptide comprising all or a portion of amino acid residues 143-168 of human MBP, a peptide comprising all or a portion of amino acid residues 142-167 of human MBP and a peptide comprising all or a portion of amino acids residues 13-25 of human MBP. Sequences of selected peptides are shown in Figure 4. Any of these peptides may be modified as described or may extend upstream or downstream from their carboxy or amino termini so long as they maintain their antigenic quality of comprising at least one T cell epitope.

As a result of the work described herein it has been discovered that a combination of an antigenic peptide derived from MBP and IFN-β, when administered in a therapeutic regimen, has a synergistic effect (Fig. 1c) which surprisingly diminishes the clinical symptoms of EAE in mice to a far greater extent than the effect of each on mitigating the symptoms of EAE when administered alone

(Figs. 1a-b), and which is greater than what one would expect for a merely additive effect of the peptide plus IFN-β.

As EAE serves as a mouse model of human MS and is induced by MBP, it is expected that a similar effect would also be seen in humans. Therefore, the present invention provides a method of treating individuals who have multiple sclerosis or are susceptible to developing multiple sclerosis, which comprises administering an effective amount of an antigenic peptide derived from MBP in non-immunogenic form (i.e. without adjuvant) in a therapeutic regimen which also includes the administration of IFN-β.

Administration of a composition comprising at least one antigenic peptide of MBP in a therapeutic regimen which includes administration of IFN-β can be carried out using known procedures at dosages and for periods of time to effectively reduce, eliminate or prevent the symptoms associates with multiple sclerosis. Effective amounts of either antigenic peptide or IFN-β when administered together in a therapeutic regimen vary according to factors such as the degree of sensitivity and susceptibility of the individual to MS, the age, sex, and weight of the individual, and the ability of the antigenic MBP peptide to elicit an antigenic response in the individual. The active compounds (i.e. the MBP peptide or composition thereof and IFN-β) may be administered in a convenient manner such as by injection (subcutaneous, intravenous etc.), oral administration, inhalation, transdermal application or rectal administration. Depending on the route of administration, the active compound may be coated with a material to protect the compound from the action of enzymes, acids and other natural conditions which may inactivate the compound.

For example, preferably about 1 μg-3mg and more preferably about 20-500 μg of antigenic peptide derived from MBP per dosage unit may be administered by injection. Preferably, a dosage unit of 100-10,000 units of IFN-β may be administered by injection. The dosage regimen of these two compounds may be adjusted to provide the optimum therapeutic response. For example, IFN-β and a composition comprising antigenic peptide derived from MBP may be administered simultaneously or may preferably be administered at least six hours apart, preferably at least 12 hours apart, or more preferably at least 24 hours apart. The therapeutic regimen of administering both antigenic peptide and IFN-β may continue over a period of days or weeks and may be reduced or extended as indicated by the exigencies of the therapeutic situation.

The present invention also provides a novel composition comprising a physical mixture of an antigenic peptide derived from MBP and IFN-β in a

pharmaceutically acceptable carrier or diluent. This composition may be used as part of a therapeutic regimen for treating or preventing multiple sclerosis in an individual.

This invention is further illustrated by the following non-limiting example.

EXAMPLE

Synthesis of mouse MBP peptide Ac 1-11

Mouse MBP peptide Ac 1-11 was synthesized using standard Fmoc/tBoc synthesis and purified by HPLC. The amino acid sequence for peptide Ac 1-11 is as follows:

Induction of EAE

EAE was induced in 6 to 8 week old female (SJL x PL)F_1 mice (Jackson Labs, Bar Harbor, ME) by immunizing mice with 100 μg purified guinea pig MBP in CFA (GIBCO Lab., Grand Island, NY) containing 400 μg H37RA strain M. tuberculosis (DIFCO Lab., Detroit, MI) subcutaneously at the base of the tail. 200 ng Pertussis Toxin (JHL BIOSCIENCE, Lenexa, Kansas) was given twice intravenously (i.v.) on the day of immunization and also 48 hours later. Mice were monitored daily for disease symptoms and were scored for disease severity on the following scale 0=no clinical signs of EAE, 1=limp, unresponsive tail, 2=partial hindlimb paralysis, 3=complete hindlimb paralysis, 4=partial to complete forelimb paralysis and 5=moribund. Data are expressed as the mean of the disease severity score on each day including all the animals in the group. Mice were followed for 26 days. Once a mouse died of EAE, a score of 5 was included in calculations for all subsequent days.

Effect of IFN-β on EAE

In a titration experiment for the purposes of determining the effects of various dosages of IFN-β on EAE (Fig. 2). One group of mice was treated intraperitoneally with PBS on days 9, 13, and 16 (control) after EAE induction, one group of mice were treated with 10,000 units of IFN-β on days 9, 13, and 16 (open circle) and one group of mice were treated with 2,000 units of IFN-β on days 9, 13, and 16 (closed circle). As shown in Fig. 2, the symptoms of EAE are similar at each time point for both dosages of IFN-β, thereby indicating that the lower dosage would be suitable for experiments with IFN-β and is a preferred dosage as the chances of toxicity due to a higher dose of IFN-β are less likely. 2000 units of IFN-β were then used in the remaining experiments shown in Figs 1a-1c as this dosage showed improvement in clinical score.

As shown in Fig 1a a control group of mice was treated with PBS and another group of mice were treated with 2000 units of IFN-β i.p. on days 9, 12, 16, and 20. As shown in Fig. 1a, the group treated with IFN-β only had slightly less severe symptoms during the time course as those of the control group.

Effect of mouse MBP peptide Ac 1-11 on EAE

The effect of mouse MBP peptide Ac 1-11 was determined and the results are shown in Fig. 1b. One group of mice was treated i.p. with PBS on days 10, 13, 17, and 21 (control) after EAE induction, and one group of mice was treated i.v. with 250 nmol of peptide Ac 1-11 on days 10, 13, 17, and 21. The mice were monitored as described above. As shown in Fig 1b, the mice treated with Ac 1-11 had less severe symptoms than those of the control group.

Effect of treatment with a combination of peptide Ac 1-11 and IFN-β on EAE

The effects of treatment with a combination of peptide Ac 1-11 and IFN-β are shown in Fig. 1c. One group of mice was treated i.p. with PBS (control) after EAE induction, and one group of mice was treated i.v. with 250 nmol of peptide Ac 1-11 on days 10, 13, 17 and 21 (open arrows) and treated i.p. with 2000 units of IFN-β on days 9, 12, 16, and 20. As shown in Fig. 1c, the group of mice treated with a combination of peptide and IFN-β showed a marked decrease in the severity of symptoms as compared with the control group as well as compared to treatment with either IFN-β alone or peptide alone as shown in Figs. 1a and 1b indicating a synergistic effect of the combination. Therefore, a treatment regimen which includes a combination of peptide and IFN-β provides an enhanced effect on diminishing the severity of the symptoms of EAE.

Although the invention has been described with reference to its preferred embodiments, other embodiments can achieve the same results. Variations and modifications to the present invention will be obvious to those skilled in the art and is intended to cover in the appended claims all such modifications and equivalents that follow in the true spirit and scope of the invention.

What is claimed is:

1. A method for treating multiple sclerosis in an individual comprising administering a therapeutically effective amount of at least one antigenic peptide of MBP in a therapeutic regimen which includes administering a therapeutically effective amount of IFN-β.

2. The method of claim 1 wherein said antigenic peptide of MBP and said IFN-β are administered simultaneously.

3. The method of claim 1 wherein said antigenic peptide of MBP and said IFN-β are administered at least 24 hours apart.

4. The method of claim 1 wherein said at least one antigenic peptide is selected from the group consisting of: a peptide comprising all or a portion of amino acid residues 84-106 of human MBP, a peptide comprising all or a portion of amino acid residues 84-102 of human MBP, a peptide comprising all or a portion of amino acid residues 89-101 of human MBP, a peptide comprising all or a portion of amino acid residues 140-172 of human MBP, a peptide comprising all or a portion of amino acid residues 143-168 of human MBP, a peptide comprising all or a portion of amino acid residues 142-167 of human MBP and a peptide comprising all or a portion of amino acids residues 13-25 of human MBP.

5. A composition comprising a therapeutically effective amount of at least one antigenic peptide of human MBP and a therapeutically effective amount of IFN-β in a pharmaceutically acceptable carrier or diluent.

6. A composition of claim 5 wherein said at least one antigenic peptide is selected from the group consisting of: a peptide comprising all or a portion of amino acid residues 84-106 of human MBP, a peptide comprising all or a portion of amino acid residues 84-102 of human MBP, a peptide comprising all or a portion of amino acid residues 89-101 of human MBP, a peptide comprising all or a portion of amino acid residues 140-172 of human MBP, a peptide comprising all or a portion of amino acid residues 143-168 of human MBP, a peptide comprising all or a portion of amino acid residues 142-167 of human MBP and a peptide comprising all or a portion of amino acids residues 13-25 of human MBP.

7. A method of preventing the onset of multiple sclerosis in an individual susceptible to multiple sclerosis comprising administering a therapeutically effective amount of at least one antigenic peptide of MBP in a treatment regimen which includes administering a therapeutically effective amount of IFN-β.

8. A method of claim 4 wherein said at least one antigenic peptide is modified.

9. A method of claim 4 comprising at least two antigenic peptides.

10. A composition of claim 5 wherein said at least one antigenic peptide is selected from the group consisting of: a peptide comprising all or a portion of amino acid residues 84-102 of human MBP, a peptide comprising all or a portion of amino acid residues 89-101 of human MBP, a peptide comprising all or a portion of amino acid residues 143-168 of human MBP, a peptide comprising all or a portion of amino acid residues 142-167 of human MBP and a peptide comprising all or a portion of amino acids residues 13-25 of human MBP each having the sequences shown on Figure 4.

11. An isolated MBP peptide comprising amino acid residues 142-167 as shown in Figure 4.

12. A composition comprising the isolated peptide of claim 11.

13. An isolated MBP peptide having a carboxy terminus and an amino terminus said peptide comprising amino acid residue 142-167 wherein said peptide is extended by at least one amino acid residue downstream from the carboxy terminus of said peptide.

14. The isolated peptide of claim 13 wherein said peptide maintains its antigenic quality of comprising at least one T cell epitope.

15. A composition comprising the isolated peptide of claim 13.

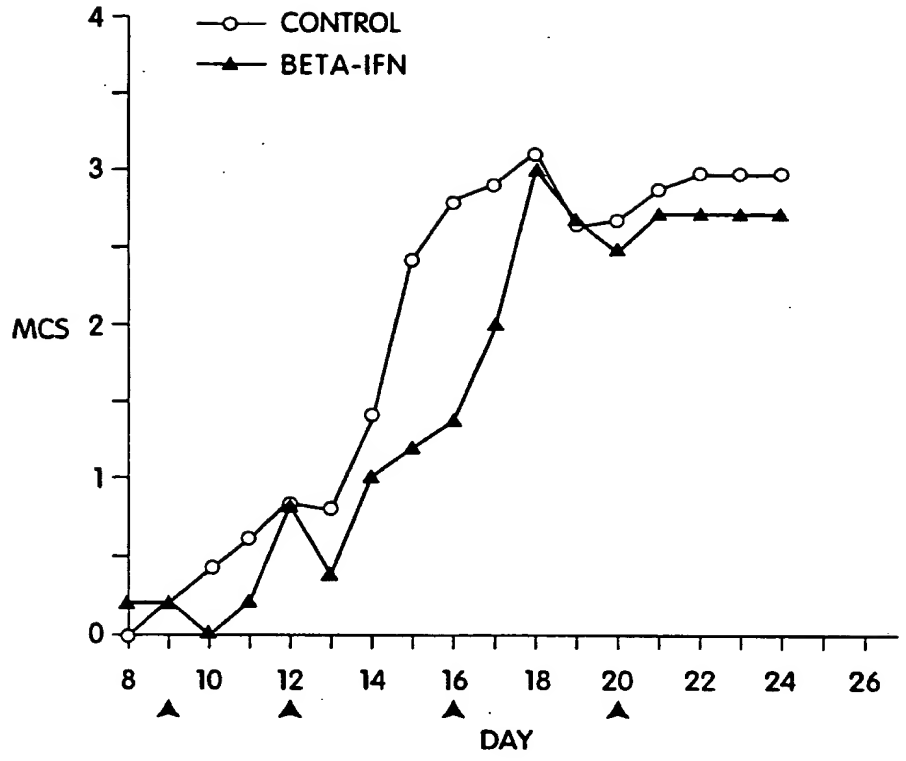
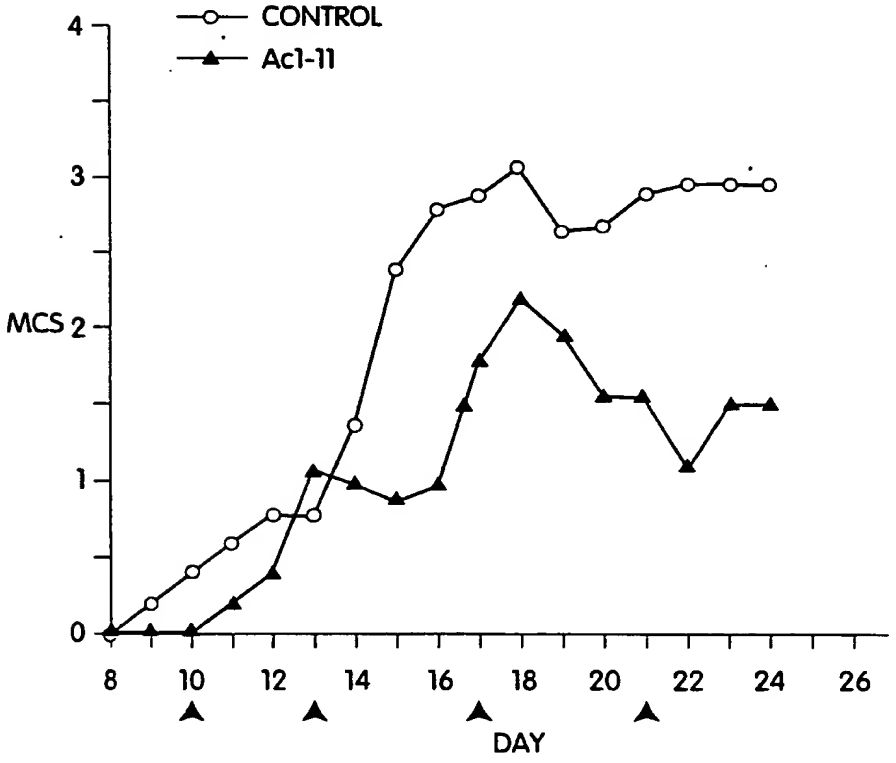

CONTROL
BETA-IFN
MCS
0
1
2
3
4
8
10
12
14
16
18
20
22
24
26
DAY

Fig. 1A


CONTROL
Ac1-11
MCS
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1
2
3
4
8
10
12
14
16
18
20
22
24
26
DAY

Fig. 1B

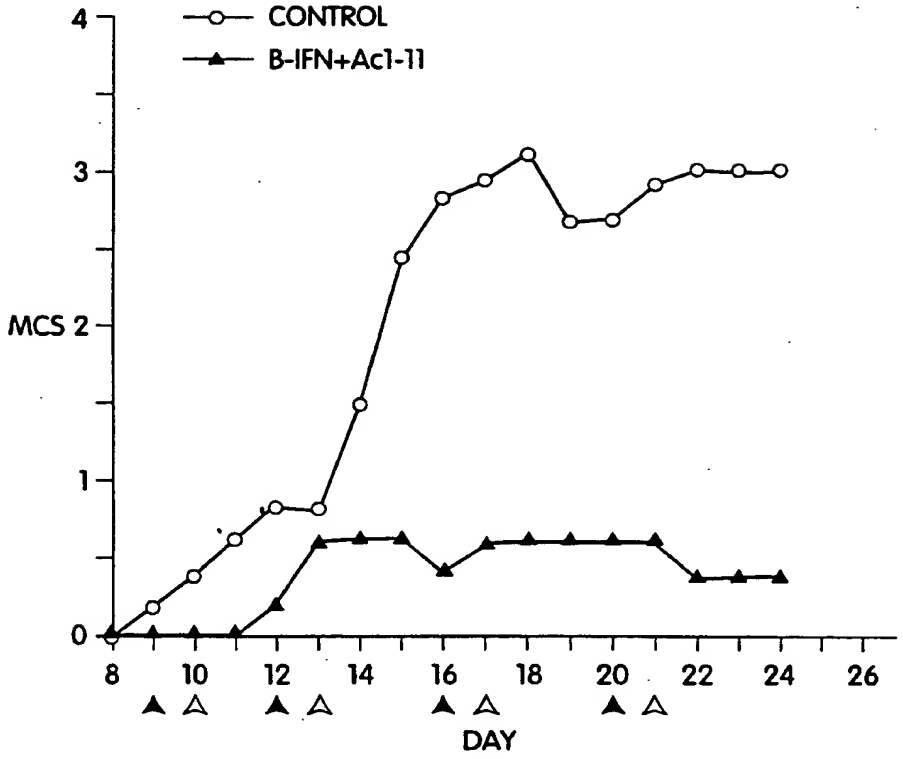

Fig. 1C

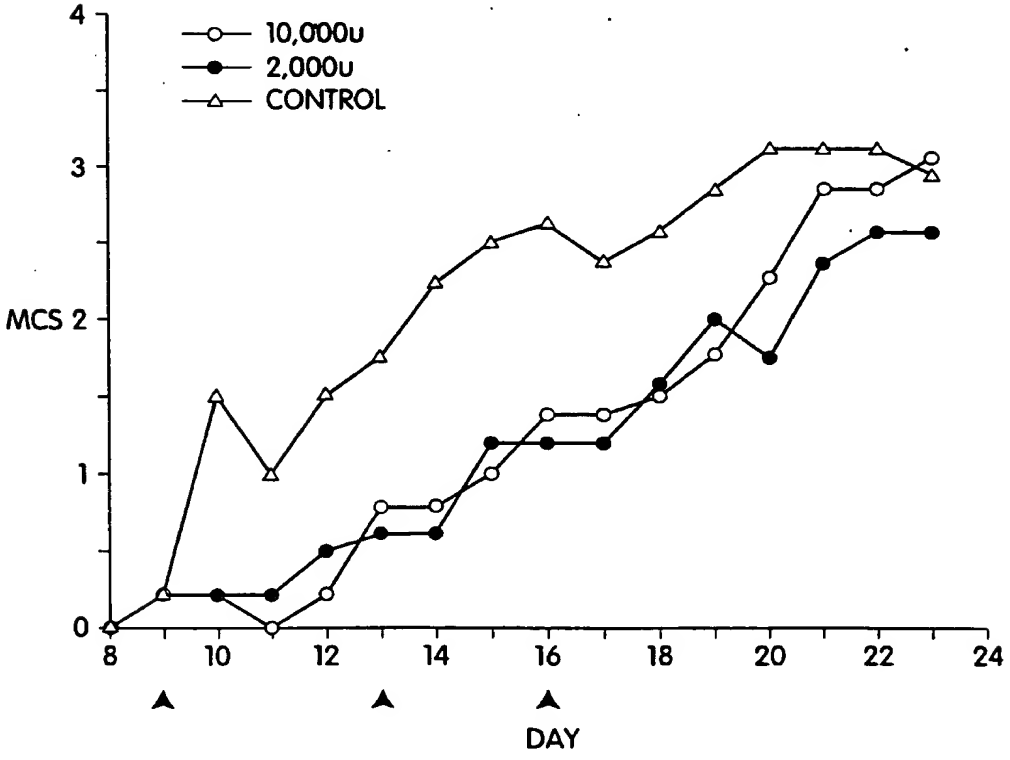

Fig. 2

A S Q K R P S Q R H[10]G S K Y L A T A S T[20]M D H A R H G
F L P[30]R H R D T G I L D S[40]I G R F F G G D R G[50]A P K R G
S G K D S[60]H H P A R T A H Y G[70]S L P Q K S - H G R[80]T Q
D E N P V V H F[90]F K N I V T P R T P[100]P P S Q G K G R G
L[110]S L S R F S W G A E[120]G Q R P G F G Y G G[130]R A S D Y K
S A H K[140]G F K G V D A Q G T[150]L S K I F K L - G[160]G R D
S R S G S P M A[170]R R

Fig. 3

MBP 84-102	DENPVVHFFKNIVTPRTPP
MBP 89-101	VHFFKNIVTPRTP
MBP 143-168	FKGVDAQGTLSKIFKLGGRD
MBP 142-167	FKGVDAQGTLSKIFKLGGRDSRSGS
MBP 13-25	KYLATASTMDHAR

Fig. 4